Serial No.: 09/553,993
Filed: April 20, 2000

REMARKS

Claims 1-14 are pending. Claims 1, 2, 10, and 14 are amended for technical clarity. Support for amended claim 1 is found is found within claim 1 and was amended only to clarify the subject matter. Support for amended claim 10 is found within claim 6 and was made to provide proper antecedent basis. Support is also found throughout the specification, i.e. page 19, line 23. Support for amended claim 14 is found within original claim 14 as recognized by the Examiner.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "Marked-up Amended Claims". For the Examiner's convenience a clean copy of the currently pending claims is appended hereto as Appendix A.

Claim 2 is objected to due to missing punctuation. Claim 2 is amended. Support for amended Claim 2 is found within original claim 2 as it was a grammatical error.

Claims 1-14 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite.

Claims 1-14 are rejected as being unpatentable over Barany et al. (U.S.P.N. 6,027,889) in light of Walt et al. (U.S.P.N. 6,023,540).

Claims 1-14 are provisionally rejected under the judicially created doctrine of double patenting.

Claim objection:

The Applicants submit that the amended claim 2 is now in appropriate form and that the objection should be withdrawn. The Applicants thank the Examiner for noting the mistake.

Rejection of Claims 1-14 under 35 U.S.C. § 112, second paragraph

The Examiner asserts that the claims are indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Without necessarily agreeing with the propriety of the rejections, items (a), (b), (c), (e), and (f) have been amended for technical clarity in accord with the suggestions that the Examiner provided. The Applicants submit that the claims are no longer indefinite and request that the

rejection be withdrawn. The Applicants thank the Examiner for the useful advice.

The Item (d) has not been amended. The Examiner asserts that claim 6 is indefinite because the phrase "by chemical synthesis" is not defined in the specification and therefore it is unclear how the adapter is attached.

As a preliminary matter, Applicants submit that such methods are well known in the art and thus need not be explicitly described. Additionally, Applicants direct the Examiner's attention to the section starting on p91, line 3 entitled, "Attachment of Target Sequences to Arrays" which describes several general techniques for attachment. In particular, "..adapter sequences are added to the primers of the reaction...during the chemical synthesis of the primers." (p91,92 line 33-1) "Alternatively, the adapter sequence can be added enzymatically." (p92, line 4) "...the adapter can be attached to the target after synthesis...either covalent or non-covalent." (p92, lines 4-6) As such, examples of standard methods of chemical synthesis are provided so that one skilled in the art can understand the essential elements of chemical synthesis required for the current invention.

Rejection of Claims 1-14 under 35 U.S.C. §103(a)

Barany et al. describe a method of detecting a nucleic acid sequence involving attaching an adapter nucleic acid sequence to an oligonucleotide ligation assay probe, to form a ligated product which is detected in an array. It should be noted that Barany et. al. references high density ordered arrays, capable of identification of thousands of sequences at a time; see for example the Pease et al. article, a copy of which is attached as Exhibit A. As acknowledged by the Examiner, Barany et al. does not describe a population of microspheres as a component of the array.

Walt et al. teach a different method for detecting nucleic acid sequences using arrays comprising a substrate with a patterned surface comprising discrete sites, and a population of microspheres with capture probes.

The Examiner asserts that Claims 1-14 are unpatentable over Barany et al., (U.S.P.N. 6,027,889, filed 28 May 1997) in light of Walt et al. (U.S.P.N. 6,023,540, filed 14 May 1997). The Applicants respectfully traverse.

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As the Examiner is aware, for an invention to be obvious there must be a suggestion in the references to combine the cited references. (*see generally*, M.P.E.P. §2143). This element is lacking from the two references cited by the Examiner.

As regards the Examiner's first point, the Applicants respectfully point out that Barany et al. already references high density, ordered arrays, as outlined above. Therefore there is no "expected benefit", as Barany already utilizes such arrays. Barany et al. does not motivate one to switch from one system, e.g. an ordered array, to another system, a random array which requires additional steps to ascertain which sequences are at each location.

The Applicants remind the Examiner that the proposed modification can not change the principle of operation of the primary reference (M.P.E.P §2143.01). Even if the two references suggested an invention with microbeads and an array based sequence detection, the teachings of Walt et al. would change the principle of the array of Barany et al. While Walt et al. teaches a type of array, it is a randomly organized array system, requiring a decoding step to identify the sequences on each bead. In contrast, Barany et al. teach an ordered, addressable array system. While the combination may be possible and such a combination may not prevent the previous art from functioning, such a combination is not allowed by the M.P.E.P. because it changes the principle of operation of the primary reference, namely an ordered addressable system would have to be turned into a randomly organized system. (See *In re Ratti*, 270 F.2d 810 (CCPA 1959) holding that a combination of references in which the primary reference taught "resiliency" but the patentee taught "rigidity" was inappropriate since the combination, while suggesting a rigid structure, would alter the principle of the primary reference.)

The Examiner asserts that the motive for combining the above two inventions would be for the expected benefit of individual identification of i) thousands of captured target sequences using an apparatus which is ii) easy to manufacture and use, as taught by Walt et al. on column 3, lines 17-30.

Additionally, while the Examiner's assertion that the technique of Walt et al. is "easy to manufacture and use" is correct, this advantage is taken out of context. It is easy to manufacture and use only in relation to two previous patents which examined chemical functionalities at the end of a fiberoptic, without the use of beads. Thus, while such a statement may qualify as motive for converting from a fiberoptic beadless system to a fiberoptic system with beads, it is irrelevant for combining a hybridization based sequencing technique with a fiberoptic system–regardless of

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whether or not it has beads.

Thus, the references, taken alone or in combination, do not motivate one of skill in the art to combine the references, and thus a prima facie case of obviousness has not been established. While the above arguments were directed to claims 1 and 14, the Applicants remind the Examiner that if the independent claims, upon which there are dependent claims, are nonobvious, that the dependent claims therefrom are nonobvious. (M.P.E.P. 2143.03, *In re Fine*, 837 F.2d 1071 (Fed Cir. 1988))

Provisional Rejection of Claims 1-14 for Double Patenting

Claims 1-14 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-12 and 15-16 of copending Application No. 09/535,854.

In response, Applicants respectfully request the Examiner to hold this rejection in abeyance until there is an indication of otherwise allowable subject matter.

Applicants submit that the claims are now in condition for allowance and early notification to that effect is requested. If the Examiner feels there are further unresolved issues, the Examiner is requested to phone the undersigned at (415) 781-1989.

Respectfully submitted,

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Date: November 19, 2001

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Filed: April 20, 2000

Marked-up Amended Claims

We claim:

1. (Amended) A method of detecting a target nucleic acid sequence, said method comprising:
   a) attaching a first adapter nucleic acid to a first target nucleic acid sequence to form a modified first target nucleic acid sequence;
   b) contacting said modified first target nucleic acid sequence with an array comprising:
      i) a substrate with a patterned surface comprising discrete sites; and
      ii) a population of microspheres comprising at least a first subpopulation comprising a first nucleic acid capture probe which hybridizes to said first adapter nucleic acid, ~~such that said capture probe and said modified first target nucleic acid sequence form a hybridization complex;~~ wherein said microspheres are distributed on said patterned surface at said discrete sites; and
   c) detecting the presence of said modified first target nucleic acid sequence as an indication of the presence of said first target nucleic acid sequence.

2. (Amended) The method according to claim 1 further comprising:
   a) attaching a second adapter nucleic acid to a second target nucleic acid sequence to form a modified second target nucleic acid sequence;
   b) contacting said modified second target nucleic acid sequence with said array, wherein said population of microspheres comprises at least a second subpopulation comprising a second nucleic acid capture probe, which hybridizes to said second adapter nucleic acid ~~such that said second capture probe and said modified second target nucleic acid sequence form a hybridization complex~~; and
   c) detecting the presence of said modified second target nucleic acid sequence as an indication of the presence of said second target nucleic acid sequence.

3. The method according to claim 1, wherein said attaching is by an amplification reaction.

4. The method according to claim 3, wherein said amplification reaction is the polymerase chain reaction (PCR).

5. The method according to claim 3, wherein said amplification reaction is the oligonucleotide ligation amplification reaction (OLA).

6. The method according to claim 1, wherein said attaching is by chemical synthesis.

7. The method according to claim 1, wherein said modified target nucleic acid sequence comprises a label.

8. The method according to claim 6, wherein said label is a fluorescent label.

9. The method according to claim 6, wherein said adapter nucleic acid is labeled.

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10. The method according to claim 6, wherein said target nucleic acid ~~segment~~ sequence is labeled prior to said attaching.

11. The method according to claim 1, wherein said detecting is done by hybridizing a label probe to said modified target nucleic acid sequence.

12. The method according to claim 1, wherein said substrate is a fiber optic bundle.

13. The method according to claim 1, wherein said discrete sites comprise wells.

14. (Amended) A method of detecting a target nucleic acid sequence comprising:
a) hybridizing a first primer to a first portion of a target sequence, wherein said first primer further comprises an adapter sequence;
b) hybridizing a second primer to a second portion of said target sequence;
c) ligating said first and second primers together to form a modified primer;
d) contacting said adapter sequence of said modified primer with an array comprising:
i) a substrate with a surface comprising discrete sites; and
ii) a population of microspheres comprising at least a first subpopulation comprising a first nucleic acid capture probe, that hybridizes to said adapter sequence, ~~such that said first capture probe and said modified primer form a hybridization complex;~~ wherein said microspheres are distributed on said surface; and
e) detecting the presence of said modified primer, to thereby detect said target nucleic acid sequence.